988,001

PATENT SPECIFICATION

NO DRAWINGS

988,001

Date of Application and filing Complete Specification: Aug. 9, 1961.
No. 28785/61.
Application made in Switzerland (No. 9397) on Aug. 19, 1960.
Application made in Switzerland (No. 11974) on Oct. 26, 1960.
Application made in Switzerland (No. 967) on Jan. 27, 1961.
Application made in Switzerland (No. 1891) on Feb. 16, 1961.
Complete Specification Published: March 31, 1965.

SPECIFICATION NO. 988001

By a direction given under Section 17 (1) of the Patents Act 1949 this application proceeded in the name of WESTMINSTER BANK LIMITED, of 41, Lothbury, London, E.C.2., a British company.

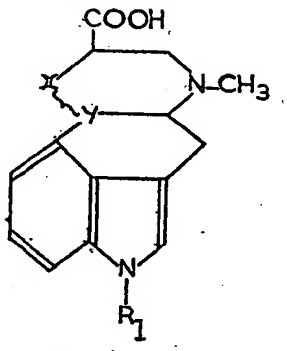
THE PATENT OFFICE

D 43146/5

Canadian Body Corporate, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

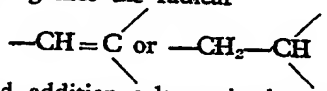
The present invention relates to new lysergic acid and dihydrolysergic acid derivatives substituted in the 1-position and to processes for their production.

The present invention provides compounds of the general formula I,



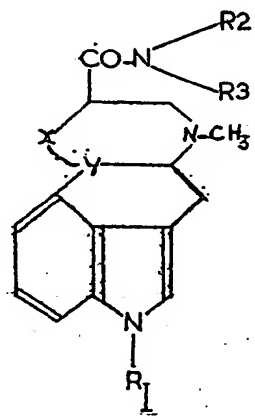
I

in which R_1 signifies an alkyl radical containing from 1 to 4 carbon atoms inclusive, a monocyclic aralkyl radical containing from 7 to 10 carbon atoms inclusive or an alkenyl radical containing from 2 to 4 carbon atoms inclusive, and $\overset{\frown}{x\ y}$ signifies the radical



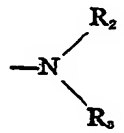
their acid addition salts and pharmaceutical compositions containing, in addition to an inert carrier, a compound I and/or said salt.

The present invention also provides a process for the production of a compound of general formula I, which comprises reacting a compound of general formula II,



II

in which R_1 and $\overset{\frown}{x\ y}$ have the above significance and each of R_2 and R_3 signifies a hydrogen atom, an alkyl radical containing from 1 to 4 carbon atoms inclusive or a hydroxyalkyl radical containing from 1 to 4 carbon atoms inclusive with the proviso that R_2 and R_3 need not be dissimilar or the radical



signifies the tripeptide radical of a natural water insoluble ergot alkaloid, is saponified with an alkali metal hydroxide, and, when the salt is desired, salification is effected with an organic or inorganic acid.

The invention further provides a process for

[*Price 4s. 6d.*]

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Index at acceptance:—C2 C(3A10A4G, 3A10A5A1, 3A10A5A2, 3A10A5C, 3A10A5F, 3A10A5K)

Int. Cl.:—C 07 d

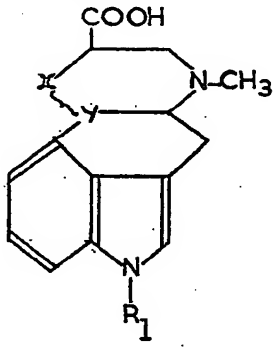
COMPLETE SPECIFICATION

Improvements in or relating to Lysergic Acid Derivatives

We, SANDOZ PATENTS LIMITED, of 590 Jarvis Street, Toronto 5, Ontario, Canada, a Canadian Body Corporate, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

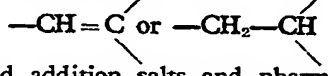
The present invention relates to new lysergic acid and dihydrolysergic acid derivatives substituted in the 1-position and to processes for their production.

The present invention provides compounds of the general formula I,



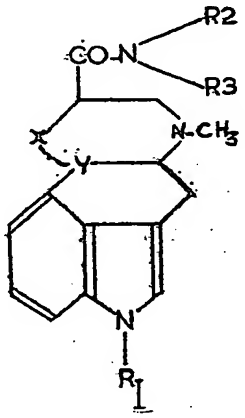
I

in which R_1 signifies an alkyl radical containing from 1 to 4 carbon atoms inclusive, a monocyclic aralkyl radical containing from 7 to 10 carbon atoms inclusive or an alkenyl radical containing from 2 to 4 carbon atoms inclusive, and $\overset{x}{\overset{y}{}}$ signifies the radical



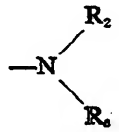
their acid addition salts and pharmaceutical compositions containing, in addition to an inert carrier, a compound I and/or said salt.

The present invention also provides a process for the production of the compounds I and their acid addition salts, characterized in that a compound of general formula II,



II

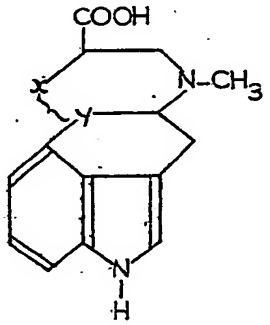
in which R_1 and $\overset{x}{\overset{y}{}}$ have the above significance and each of R_2 and R_3 signifies a hydrogen atom, an alkyl radical containing from 1 to 4 carbon atoms inclusive or a hydroxyalkyl radical containing from 1 to 4 carbon atoms inclusive with the proviso that R_2 and R_3 need not be dissimilar or the radical



signifies the tripeptide radical of a natural water insoluble ergot alkaloid, is saponified with an alkali metal hydroxide, and, when the salt is desired, salification is effected with an organic or inorganic acid.

The invention further provides a process for

the production of the compounds I and their acid addition salts, characterized in that a lysergic acid or a dihydrolysergic acid of the general formula III,



III

in which x y has the above significance, is treated with an alkali metal amide in liquid ammonia and the resulting alkali metal salt is reacted with an organic halogen compound of general formula

$$R_1—Hal$$

in which R_1 has the above significance, and Hal signifies a chlorine, bromine or iodine atom. and, when the salt is desired, salification is effected with an organic or inorganic acid.

The first process may be effected as follows:—

A solution of compound II in water, alcohol or a mixture of both is heated with an alcoholic alkali metal hydroxide solution, e.g. lithium hydroxide, sodium hydroxide or potassium hydroxide, preferably at the boiling point of the solvent. Due to the instability of compound II, the reaction is advantageously performed in an atmosphere of nitrogen. Should compound II contain a tripeptide radical of a natural, water insoluble ergot alkaloid, an excess of alkali metal hydroxide is necessary for the success of the reaction, otherwise the theoretical quantity of alkali metal hydroxide suffices, though the use of an excess improves the yield. The alcohol is then evaporated from the reaction mixture, if necessary after the addition of water, and the mixture then reacted with a quantity of acid which is exactly equivalent to the amount of the alkali metal hydroxide used, the crystalline compound I which is generally mixed with impurities and decomposition productions, separating.

When the unsaturated lysergic acid derivatives of general formula II,

(i.e. x y = —CH = C)

are saponified, a mixture of the lysergic acid and isolysergic acid derivatives substituted in the 1-position is always obtained. The mixture may be separated by dissolving in a suitable acid and precipitating with a base, by dissolving in a base and fractionally precipitating with an acid or by means of a combination of the two operations or by fractional recrystallisation if desired in the form of a salt or by absorption analysis, preferably on cellulose.

The second process of the invention may be effected in such a way that an alkali metal, preferably sodium, is oxidised with ferric nitrate in liquid ammonia to form the alkali metal amide, e.g. sodium amide. The dry acid III is added in a high vacuum and after a few minutes the resulting alkali metal salt is mixed with the desired organic halogen compound R_1—Hal. 2 to 10, preferably 3 to 5 atoms of alkali metal and 2 to 10 mol, preferably 4 to 6 mol of the organic halogen compound are used per mol of acid.

The ammonia may be evaporated a few minutes after addition of the organic halogen compound. To isolate the compound I the reaction mixture is shaken between water and ether and the aqueous phase filtered through a talc layer. The procedure which is then followed depends on the acid and the organic halogen compound used. The isolation of 1 - methyl - D - lysergic acid in pure, crystalline form is particularly simple, it being sufficient for the aqueous solution to be brought to a pH value of 4.5 to 5 with acetic acid. Otherwise, the aqueous solution may be evaporated to dryness and methanol poured over the dry residue, the inorganic salts and the small quantity of 1 - methyl - isolysergic acid present going into solution and the 1 - methyl - D - lysergic acid remaining undissolved.

It is surprising that the above process gives good results when free lysergic acid or dihydrolysergic acid is used as a starting material, as side reactions (e.g. esterification, substitution in the 8-position of the lysergic acid structure and isomerisation) were to be expected. Furthermore, it was to be expected that the reaction product would be difficult to isolate in the pure state.

It has now surprisingly been found that the above process can be applied to such complicated molecules as the above compounds III and that good yields result.

At room temperature the compounds I are solid, easily crystallisable substances. They are very slightly soluble in water and practically insoluble in non-polar solvents. In polar solvents, e.g. alcohol, they are fairly to difficultly soluble. They are ampholytes and hence readily soluble in alkalis and inorganic acids. With Keller's colour reagent and Van Urk's colour reagent they give a characteristic colour reaction.

The compounds I may be used as pharmaceuticals or as intermediate products in the production of pharmaceuticals, e.g. in the production of 1 - methyl - lysergic acid - butanolamide - (2^1).

In the following non-limitative examples, all temperatures are given in degrees Centigrade. The melting points are uncorrected.

EXAMPLE 1

1 - methyl - dihydro - D - lysergic acid.

A solution of 9.5 g of 1 - methyl - dihydro - ergocryptine in 240 cc of ethanol and 240 cc of 4N 50% methanolic potassim hydroxide is boiled at reflux for 20 hours. The alcohol is then distilled off, the remaining aqueous solution filtered and 480 cc of 2N hydrochloric acid are added. After standing for a few hours at 0° the separated 1 - methyl - dihydro - D - lysergic acid is filtered off, washed with water and dried in a vacuum at 80°.

For the purpose of purification the compound is dissolved in a 10% methane sulphonic acid, the solution filtered through a talc layer until clear and the solution neutralised to a pH value of 7 with 2N sodium hydroxide and inoculated. The 1 - methyl - dihydro - D - lysergic acid crystallises in the form of small colourless prisms. Melting point 335° (decomposition).

$$[\alpha]_D^{20} = -111 \pm 20°$$

(c = 0.05 in pyridine).

The compound only becomes slightly soluble in more than 1000 parts of pyridine. In water, alcohol and methanol it is practically insoluble at 20°.

$$[\alpha]_D^{20} = -58.3°$$

(c = 1.0 in 0.1N aqueous methane sulphonic acid solution).

Both rotations are measured with a photoelectric Zeiss-polarimeter, the D-line being extrapolated.

EXAMPLE 2

1 - methyl - D - isolysergic acid

10 g of 1 - methyl - D - lysergic acid - D - propanolamide - (2[1]) are added to a solution of 5 g of potassium hydroxide in 20 cc of water and 20 cc of ethanol and the mixture heated under reflux in an atmosphere of nitrogen for 6 hours. The solution is then shaken four times with 50 cc of ethyl acetate and the aqueous phase acidified with 2N sulphuric acid whilst the solution is being cooled. The separated, crude, red and partly oily mixture of 1 - methyl - D - lysergic acid and 1 - methyl - D - isolysergic acid is filtered with suction and washed with water. The mixture is dissolved in 20 cc of glacial acetic acid and then evaporated in a vacuum until the solution has become syrupy. After the addition of 5 cc of water the mixture of the two acids starts to crystallise as a light grey crystalline powder. The 1 - methyl - D - isolysergic acid portion may be separated in the following manner:

The mixture is dissolved in 50 cc of concentrated ammonia, the solution filtered through a talc layer and dry ice added. The ammonium salt of the 1 -methyl - D - isolysergic acid starts to crystallise after a short time, is filtered with suction and washed with a minimum quantity of water. (The ammonium salt of 1 - methyl - D - isolysergic acid is highly soluble in water). The compound is then dissolved in 2.5 cc of water and a few drops of glacial acetic acid are added, whereupon the free 1 - methyl - D - isolysergic acid separates as a light grey crystalline powder having a melting point of 215° (decomposition)

$$[\alpha]_D^{20} = +330° \pm 10°$$

(c = 0.2 in methanol).

Keller's colour reaction: blue-violet.

EXAMPLE 3

1 - benzyl - 9,10 - dihydro - D - lysergic acid.

0.5 g of 1 - benzyl - dihydro - ergocryptine with 12.5 cc of 4N potassium hydroxide are heated at reflux in 50% methanol and 12.5 cc of ethanol for 16 hours. The reaction mixture is then neutralised with 41 cc of N hydrochloric acid, the solution filtered and the precipitate washed with water. The almost completely crystalline precipitate, obtained after rubbing with some methanol, is then dissolved in 1 cc of glacial acetic acid and the solution evaporated to dryness. Upon dissolving the residue in 1 to 2 cc of water, small prisms containing half a mol of water of crystallisation and melting at 217 to 222°, are obtained.

$$[\alpha]_D^{20} = -106°$$

(c = 0.5 in pyridine).

Keller's colour reaction: blue.

EXAMPLE 4

1 - methyl - D - lysergic acid.

A solution of 1.2 g of sodium in 200 cc of liquid ammonia is oxidised with ferric nitrate to sodium amide, 4.7 g of D - lysergic acid are added and the brown solution mixed with a solution of 10 g of methyl iodide in 10 cc of ether after 5 minutes. After a further 5 minutes the ammonia is evaporated in the absence of moisture, finally in a vacuum, and the dry residue shaken between 250 cc of ether and 400 cc of water. The aqueous phase is filtered through a talc layer, evaporated to dryness, the dry residue warmed slightly together with 100 cc of methanol and the undissolved 1 - methyl - D - lysergic acid filtered off. For the purpose of removing dark impurities and small quantities of D - lysergic acid, the mixture is dissolved in methanolic alkali, filtered through a talc layer and the mixture brought to a pH value of 6 by adding acetic acid dropwise, the 1 - methyl - D - lysergic acid crystallising as an almost colourless crystalline powder. Melting point: 237 to 239°

$$[\alpha]_D^{20} = +120°$$

(c = 0.5 in 0.1N aqueous methane sulphonic acid).

Only in 1500 to 2000 parts of pyridine does the compound dissolve. Keller's colour reaction: blue.

EXAMPLE 5

1 - Allyl - D - lysergic acid

A solution of 1.4 g of sodium in 200 cc of liquid ammonia is oxidised with ferric nitrate to sodium amide and 5.0 g of D - lysergic acid are added to the decolourised solution. After 5 minutes a mixture of 10 g of allyl bromide and 20 cc of ether is added to the solution. After a further 5 minutes the ammonia is evaporated and the residue absorbed in about 100 cc of water. The solution is then filtered from the ferric hydroxide, the filtrate brought to a pH value of 4 to 6 by adding acetic acid, the solution decanted from the separated oily 1 - allyl - D - lysergic acid and the compound recrystallised from methanol. Melting point: 209 to 211°

$[\alpha]_D^{20} = +99°$
(c = 0.5 in 0.1N methane sulphonic acid).

Keller's colour reaction: grey-blue.

EXAMPLE 6

1 - ethyl - D - lysergic acid

In a manner analogous to that described in example 5, the 1 - ethyl - D - lysergic acid results from 5 g of D - lysergic acid, 1.4 g of sodium and 12 g of ethyl iodide in 200 cc of liquid ammonia. Prisms from methanol. Melting point 219 to 220°.

$[\alpha]_D^{20} = +113°$
(c = 0.5 in 0.1N methane sulphonic acid).

Keller's colour reaction: blue.

EXAMPLE 7

1 - *n* - propyl - D - lysergic acid

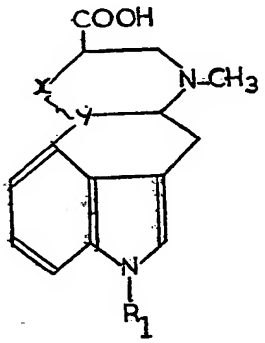
In an analogous manner to that described in example 5, 1 - *n* - propyl - D - lysergic acid results from 10 g of D - lysergic acid, 2.8 g of sodium and 28.5 g of *n* - propyl iodide in 400 cc of liquid ammonia. Melting point: 206 to 208°

$[\alpha]_D^{20} = +102°$
(c = 0.5 in 0.1N methane sulphonic acid).

Keller's reaction: blue.

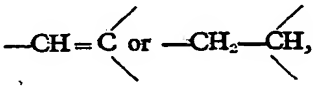
WHAT WE CLAIM IS:—

1. A process for the production of compounds of the general formula I,

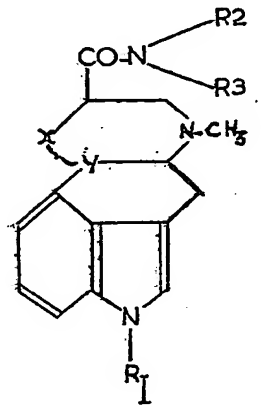


I

in which R_1 signifies an alkyl radical containing from 1 to 4 carbon atoms inclusive, a monocyclic aralkyl radical containing from 7 to 10 carbon atoms inclusive or an alkenyl radical containing from 2 to 4 carbon atoms inclusive, and $\overset{\frown}{x\ y}$ signifies the radical

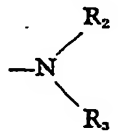


and their acid addition salts, characterized in that a compound of general formula II,



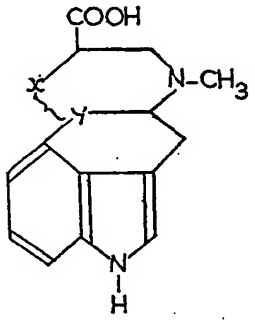
II

in which R_1 and $\overset{\frown}{x\ y}$ have the above significance and each of R_2 and R_3 signifies a hydrogen atom, an alkyl radical containing from 1 to 4 carbon atoms inclusive or a hydroxyalkyl radical containing from 1 to 4 carbon atoms inclusive with the proviso that R_2 and R_3 need not be dissimilar or the radical



signifies the tripeptide radical of a natural water insoluble ergot alkaloid, is saponified with an alkali metal hydroxide and, when the salt is desired, salification is effected with an organic or inorganic acid.

2. A process for the production of compounds I stated in claim 1 and their acid addition salts, characterized in that a lysergic acid or a dihydrolysergic acid of the general formula III,



III

in which $\overset{\frown}{x\ y}$ has the same significance as in claim 1, is treated with an alkali metal amide in liquid ammonia and the resulting alkali metal salt is reacted with an organic halogen compound of general formula

R_1—Hal

in which R_1 has the same significance as in claim 1, and Hal signifies a chlorine, bromide or iodine atom, and, when the salt is desired, salification is effected with an organic or inorganic acid.

3. A process for the production of compounds of general formula I stated in claim 1 and their acid addition salts, substantially as herein described with reference to any one of the examples.

4. The compounds of the general formula I stated in claim 1 and their acid addition salts, whenever produced by the process claimed in any one of the claims 1 to 3.

5. The compounds of the general formula I stated in claim 1 and their acid addition salts.

6. 1 - methyl - dihydro - D - lysergic acid and its acid addition salts.

7. 1 - methyl - D - isolysergic acid and its acid addition salts.

8. 1 - benzyl - 9,10 - dihydro - D - lysergic acid and its acid addition salts.

9. 1 - methyl - D - lysergic acid and its acid addition salts.

10. 1 - allyl - D - lysergic acid and its acid addition salts.

11. 1 - ethyl - D - lysergic acid and its acid addition salts.

12. 1 - *n* - propyl - D - lysergic acid and its acid addition salts.

13. Pharmaceutical compositions containing, in addition to an inert carrier, a compound claimed in any one of the claims 4 to 12.

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